09/868394

PATENT COOPERATION TREATY

REC'D 15 NOV 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
KR/P32221		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04326	20/12/1999	18/12/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant SMITHKLINE BEECHAM PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Auth rity and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/06/2000	13.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weijland, A Telephone No. +49 89 2399 7490

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04326

I. Basis of th r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendm nts had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The following documents (D) are referred to in this opinion; the numbering will be adhered to the rest of the procedure:

D1: WO 96 38586 A
D2: PROC.NATL.ACAD.SCI. USA , Vol. 92, 1995, pages 3041-3045
D3: THE JOURNAL OF IMMUNOLOGY, VOL. 144, no. 2, 521-525

SECTION V

1. The subject matter of claims 1-11 is novel (Article 33(2) PCT).

   The subject matter of claim 1, relating to a method for the detection of compounds that mimics, potentiates or inhibits the physiological effect of the ob-protein, is not disclosed in the prior art documents.

2. The subject matter of claims 1-11 does not involve an inventive step (Article 33(3) PCT).

   D1 is considered to be the closest prior art. D1 (abstract) describes a method for the detection of a compound that mimics, potentiates or inhibits the physiological effects of the ob-protein comprising an ob protein activated transcription (STAT) DNA element coupled to a reporter gene. The reporter being expressed in an ob-protein responsive cell line. Claim 1 differs from D1 in that claim 1 describes the use of an endothelium derived cell line in a method for the detection of compounds that influence the ob-protein induced STAT mediated signal transduction pathway.

   The technical problem to be solved would reside in finding an alternative method for the detection of compounds that influence the physiological effect of the ob-protein.

   The skilled person, equipped with the knowledge of D1, would be motivated to use endothelium derived cell lines, since these cells show expression of the MHC class II Ag after treatment with rIFN-γ (D3, page 523, right column) and IFN-γ is known to activate certain STAT proteins (D2, abstract, Table 2). Cells containing

JAK, STAT and further proteins necessary to obtain a signal response are preferred according the method of present claim 1 (see present application page 4, lines 32-37). Thus, the use of endothelium derived cells would be a non-inventive selection from a limited number of tissue cell lines from which the skilled person would choose without resulting in any unexpected effect whatsoever.

Claims 2-7, relating to method of claim 1, consisting of alternative endothelium cell lines (claims 2-6) containing isoforms of the leptin receptor (claim 7) form non-inventive selections from which the skilled person would choose without achieving any unexpected effect (see above).

Claims 8-10 are rendered obvious by D1 (page 2, lines 11-20), which discloses

* the response element is coupled to a minimal promoter, see present claim 8.
* the response element is of the formula TT(N)nAA, see present claim 9.
* the response element has the sequence TTCCCGGAA, see present claim 10.

Dependent claim 11 does not contain any features which, in combination with the features of claim 1 to which it refers, meet the requirements of the PCT in respect of inventive step, since the sequences mentioned are mere alternatives of the sequence TT(N)nAA in which n=5, see also page 3, lines 14-21 of the present application.

SECTION VII

3. The references to non published patent applications, such as on page 1 (line 29) contravenes the requirement for the application to be self contained (see Guidelines C-II 4.17).

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 and D3 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

5. Claims 3, 4, 6 are unclear (Article 6 PCT) and insufficiently disclosed (Article 5 PCT). In said claims endothelium cell lines are identified by way of a trivial designation, which is meaningless to a person skilled in the art. Reference could be made to deposits of the cell lines which would show that they were publicly available on the filing date of this application. However, information on the deposit must either be present in the application as filed or submitted within 16 months of the priority date (Rule 13bis.4(a)(i) PCT). As neither of these requirements have been met, said claims contravene the requirements of Article 5 and 6 PCT.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
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in its capacity as elected Office

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
International application No. PCT/GB99/04326	**Applicant's or agent's file reference** KR/P32221
International filing date (day/month/year) 20 December 1999 (20.12.99)	**Priority date** (day/month/year) 18 December 1998 (18.12.98)
Applicant BRISCOE, Celia	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 June 2000 (27.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12Q 1/68 — A3

(11) International Publication Number: WO 00/37675

(43) International Publication Date: 29 June 2000 (29.06.00)

(21) International Application Number: PCT/GB99/04326

(22) International Filing Date: 20 December 1999 (20.12.99)

(30) Priority Data:
9828087.8 18 December 1998 (18.12.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BRISCOE, Celia [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, the Pinnacles, Harlow, Essex CM19 5AW (GB).

(74) Agent: RUTTER, Keith; Corporate Intellectual Property, SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(88) Date of publication of the international search report:
14 September 2000 (14.09.00)

(54) Title: REPORTER GENE ASSAY FOR COMPOUNDS WHICH MIMIC OR INHIBIT THE PHYSIOLOGICAL EFFECT OF THE OB-PROTEIN

(57) Abstract

A method for the detection of a compound that mimics, potentiates or inhibits the physiological effect of the ob–protein, which method comprises: (a) for a compound which mimics the physiological effect of the ob–protein, assessing the effect of the compound upon an ob–protein activated signal transducer and activator of transcription (STAT) DNA response element coupled to a reporter gene; or (b) for a compound which potentiates or inhibits the physiological effect of the ob–protein, assessing the effect of the compound upon the response provided by ob–protein upon an ob–protein activated STAT DNA response element coupled to a reporter gene; wherein, the response element and the reporter are expressed in an ob–protein responsive cell line or ob–protein responsive cells, which cell line is an endothelium derived cell line and which cells are endothelium derived cells.

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 99/04326

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 38586 A (SMITHKLINE BEECHAM PLC ;BEELEY LEE JAMES (GB); SMITH RICHARD ANTHO) 5 December 1996 (1996-12-05) the whole document	1,7-10
Y	WO 98 20158 A (BEELEY LEE JAMES ;SMITHKLINE BEECHAM PLC (GB)) 14 May 1998 (1998-05-14) * see especially claims 1,10-13 * the whole document	1-6,8-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2000	20/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Knehr, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SEIDEL H M ET AL: "SPACING OF PALINDROMIC HALF SITES AS A DETERMINANT OF SELECTIVE STAT (SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCIPTION) DNA BINDING AND TRANSCIPTIONAL ACTIVITY" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 92, 1 March 1995 (1995-03-01), pages 3041-3045, XP002009232 ISSN: 0027-8424 cited in the application abstract; table 2 page 3041, column 2, paragraph 5 -page 3042, column 1, paragraph 1 ---	1,8-11
Y	BONNER S M AND O'SULLIVAN M A: "Endothelial cell monolayers as a model system to investigate dengue shock syndrome" JOURNAL OF VIROLOGICAL METHODS, vol. 71, 1998, pages 159-167, XP000913818 the whole document ---	1-3,5,6
Y	O'CONNELL K A AND EDIDIN M: "A mouse lymphoid endothelial cell line immortalized by simian virus 40 binds lymphocytes and retains functional characteristics of normal endothelial cells" JOURNAL OF IMMUNOLOGY, vol. 144, no. 2, 1990, pages 521-525, XP002139414 cited in the application the whole document ---	1,2,4,5
A	GHILARDI N ET AL: "DEFECTIVE STAT SIGNALING BY THE LEPTIN RECEPTOR IN DIABETIC MICE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 93, 1 June 1996 (1996-06-01), pages 6231-6235, XP002030820 ISSN: 0027-8424 cited in the application the whole document --- -/--	

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/04326

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TARTAGLIA L A ET AL: "IDENTIFICATION AND EXPRESSION CLONING OF A LEPTIN RECEPTOR, OB-R" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 83, no. 7, 29 December 1995 (1995-12-29), pages 1263-1271, XP000602068 ISSN: 0092-8674 cited in the application the whole document	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ional Application No
PCT/GB 99/04326

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 6002396 A	18-12-1996
		BR 9608686 A	06-07-1999
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		EP 0832284 A	01-04-1998
		HU 9801744 A	28-10-1998
		JP 11505725 T	25-05-1999
		NO 975504 A	28-11-1997
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		EP 0951564 A	27-10-1999
		NO 992107 A	30-06-1999
		PL 333187 A	22-11-1999